

# **IMMUNOLOGICAL TOLERANCE TO AUTOANTIGENS AND ALLOANTIGENS IN PRIMED HOSTS : AN ACQUIRED IMMUNE PRIVILEGE**

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The term immune privilege was initially coined to interpret experimental results showing that mismatched allografts successfully survived if implanted into particular body sites such as the anterior chamber of the eye, the central nervous system, the testes or the placenta. The initial prevailing dogma was that immune privilege was an 'intrinsic' characteristic of given anatomical locations affording them the capacity to escape inflammation.

Over last years, it became clearer that immune privilege can be acquired locally in almost any tissue in response to an inflammatory insult and also following therapeutic manipulations aiming at tolerance induction. A prototypic example, having direct implications for our model, is that of organ allografts that, as shown by the group of H. Waldmann, are indefinitely accepted following a short treatment of the host with anti-T cell monoclonal antibodies to CD4 and CD8 that induce specific tolerance to the alloantigens.

Here we provide evidence that judicious use of CD3 antibodies may represent a novel approach to achieving that goal. CD3 antibodies were initially used in experimental transplantation exclusively in naive recipients and their administration at the time of transplant mostly induced non antigen-specific immunosuppression leading to prolongation of mouse skin and islet allografts survival.

Our aim has been to revisit these results building on our experience in the field of autoimmunity where CD3 antibodies reproducibly restore immune tolerance to self tissue antigens when applied at the time of ongoing autoantigen-specific cell activation and/or established disease, in other words, in primed hosts. The initial observation made in the non obese diabetic (NOD) mouse, showed that long-standing disease remission through restoration of self-tolerance could be obtained following a short low-dose CD3 antibody treatment of overtly diabetic mice. In this setting CD3 antibodies act by 'resetting' subsets of regulatory TGF-beta-dependent CD4<sup>+</sup> T cells mediating active tolerance. Plasmacytoid dendritic cells and indoleamine 2,3-dioxygenase (IDO) also play a major role in the CD3 antibody-induced tolerance.

Using a fully MHC mismatched islet allograft model, we showed that donor-specific and transferable transplant tolerance can be induced when CD3 antibody treatment is applied once priming has taken place. These data were successfully transposed to the transplantation of vascularized cardiac allografts and to the implantation of cardiac cell progenitors derived from embryonic stem cells.

These results are of both fundamental and potential clinical relevance as humanized Fc-mutated CD3 antibodies are currently in development for clinical use. Indeed, based on the data described in NOD mice, phase II and III trials completed in patients presenting new-onset autoimmune or type 1 diabetes indicated that these new generation CD3 antibodies provide longer-term benefits than can be expected from a short-course of immunosuppression.